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Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances

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Background: Fragrance mix I (FM I) and fragrance mix II (FM II) in the European baseline series are used as screening tools for fragrance contact allergy. In 2005 the European Union (EU) required labelling of 26 fragrances when present in cosmetic products. INCI nomenclature is obligatory for such labelling.

Objectives: To describe frequencies of contact allergy to these 26 fragrance substances, and to evaluate clinical relevance of these positive reactions.

Methods: Three hundred and twenty patients with eczema suspected of being contact allergy to fragrances or cosmetics were patch tested with the EU-declared fragrance chemicals, FM I and FM II.

Results: There were 76 positive reactions in 33 patients. Most reactions were to hexyl cinnamal and hydroxyisohexyl 3-cyclohexene carboxaldehyde in 3.1%, followed by *Evernia furfuracea* (2.5%) and cinnamyl alcohol (2.5%). Twelve reactions to FM I and II were not confirmed by separate ingredients. Clinical relevance of positive reactions to fragrances was certain in 20/33 (61%).

Conclusions: 10.3% of the patients had positive patch tests in the EU-list. Hydroxyisohexyl 3-cyclohexene carboxaldehyde, a component of FM II, was the most frequent allergen, followed by *Evernia furfuracea*. Since *Evernia furfuracea* is not part of FM I or FM II, relevant reactions can be missed when only the European baseline series is used.

Key words: contact allergy; European Union; fragrances; fragrance mix; patch testing. © John Wiley & Sons A/S, 2009.

Conflicts of interest: The authors have declared no conflicts.

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Introduction

Contact allergy to fragrances is a common cause of contact dermatitis. In modern society people are exposed to fragrances and other cosmetic ingredients on a daily basis. Even so-called unperfumed products may still contain fragrance ingredients. Furthermore, fragrance materials are also present in household products and industrial materials (1).

According to some studies, contact allergy to fragrances may affect up to at least 1% of the general adult population (2–5). In patients with eczema the frequency of contact allergy to fragrances is higher, probably between 6% and 14% (6). After nickel sulphate, fragrances seem to be the most common contact allergens.

The diagnosis fragrance allergy can be made by patch testing with the European baseline fragrance

mix I (FM I). FM I consists of eight different fragrances: amyl cinnamal, cinnamyl alcohol, cinnamal, eugenol, geraniol, hydroxycitronellal, isoeugenol and *Evernia prunastri*. It is assumed that the FM I detects 70–80% of the fragrance allergic patients (2, 7–9). A second fragrance mix (FM II), containing six fragrances: citral, citronellol, coumarin, farnesol, hexyl cinnamal and hydroxyisohexyl 3-cyclohexene carboxaldehyde was developed to detect patients with fragrance allergy who would have been missed with FM I alone (10). The FM II has shown to detect additional patients (about one-third) sensitive to fragrances missed by FM I (8, 11).

26 fragrance chemical (INCI nomenclature; Table 1) contact allergens listed by the relevant scientific advisory committee of the European Commission have, since (7) March 2005, been indicated

Table 1. Positive and irritant reactions to the individual fragrances of the EU-list ($n = 320$)

	Fragrance chemical (INCI)	Test concentration	FM I/ FM II	n pos	% pos	+	++	+++	n IR	% IR
1	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	2%	FM II	10	3.1	9	1	—	2	0.6
2	Cinnamyl alcohol	2%	FM I	8	2.5	5	3	—	1	0.3
	<i>Evernia furfuracea</i> ^a	2%	—	8	2.5	7	1	—	4	1.3
3	Hydroxycitronellal	2%	FM I	7	2.2	5	2	—	1	0.3
4	<i>Evernia prunastri</i>	2%	FM I	6	1.9	4	2	—	2	0.6
5	Cinnamal	1%	FM I	5	1.6	2	3	—	1	0.3
6	Eugenol	2%	FM I	4	1.3	3	1	—	1	0.3
	Isoeugenol	2%	FM I	4	1.3	2	1	1	1	0.3
7	Farnesol	5%	FM II	3	0.9	3	—	—	3	0.9
8	Amylcinnamyl alcohol	1%	—	2	0.6	2	—	—	1	0.3
	Citral	2%	FM II	2	0.6	2	—	—	0	—
	Coumarin	5%	FM II	2	0.6	2	—	—	0	—
	Geraniol	2%	FM I	2	0.6	2	—	—	2	0.6
	Hexyl cinnamal	5%	FM II	2	0.6	2	—	—	1	0.3
	Butylphenyl methylpropional	1%	—	2	0.6	2	—	—	0	—
	Linalool	10%	—	2	0.6	2	—	—	0	—
	Alpha-isomethyl ionone	5%	—	2	0.6	2	—	—	1	0.3
9	Benzyl alcohol	1%	—	1	0.3	1	—	—	1	0.3
	Benzyl salicylate	2%	—	1	0.3	1	—	—	1	0.3
	Citronellol	2%	FM II	1	0.3	1	—	—	0	—
	Methyl-2-octynoate	0.5%	—	1	0.3	1	—	—	2	0.6
10	Amyl cinnamal	2%	FM I	0	—	—	—	—	2	0.6
	Anisyl alcohol	5%	—	0	—	—	—	—	2	0.6
	Benzyl benzoate	5%	—	0	—	—	—	—	0	—
	Benzyl cinnamate	5%	—	0	—	—	—	—	0	—
	D-Limonene	2%	—	0	—	—	—	—	0	—

^ain di-ethyl phthalate. FM I, fragrance mix I; FM II, fragrance mix II; n pos, hydroxyisohexyl number of patients with positive patch test reactions; % pos, percentage of patients with positive patch test reaction; reaction pattern of positive patch test reactions (+, ++, +++); n IR, number of patients with irritant patch test reaction; % IR, percentage of patients with irritant patch test reaction.

on cosmetic ingredient labels if present at 10 parts per million (ppm) or more in leave on, or 100 ppm or more in rinse off cosmetic products. From October 2005 detergents and similar products have also been labelled. All the fragrance ingredients of FM I and FM II are included in the EU-list.

The current study investigated the frequencies of contact allergy to these 26 fragrances in patients with eczematous skin disease, and to evaluate the clinical relevance of the positive patch test reactions. Additionally, we evaluated if patch testing with the full EU-list of declared fragrances had an additional benefit in the diagnosis of contact allergy.

Materials and Methods

From April 2005 to June 2007 a total of 320 patients were interviewed and patch tested. The patients were recruited from the outpatient department of Dermatology at the University Medical Center in Groningen, the Netherlands. Selection of the patients was made according to the following criteria: patients with eczema suspected of a contact allergy to fragrances or cosmetics and eczema localized on the face, neck, hands, axillae, genital area, or generalized eczema.

All 320 patients were tested with the series of 26 EU fragrance ingredients that are labelled. Additionally, the European baseline series (TRUE[®] test, Mekos laboratories, Denmark), which includes FM

I, was tested in 295 patients, and the FM II (Hermal/Trolab, Reinbek, Germany) was tested in 227 patients. The fragrance compounds were obtained from Hermal/Trolab and from other international suppliers (International Flavors & Fragrances, USA; Robertet, France; Givaudan, Switzerland, Milenium Speciality Chemicals Inc., USA; Bedoukian Research Inc., USA; Rhodia, France; Symrise, Germany and Firmenich, Switzerland). All fragrances were dissolved in petrolatum, except for *Evernia furfuracea* which was dissolved in di-ethyl phthalate (Table 1). Patch tests were performed and read according to the guidelines of the International Contact Dermatitis Research Group (ICDRG) (12). The patches were applied for 2D. Final reading was done on D3. (7, 13). Reading of doubtful reactions was done up to D7 after the application of the patch test material. The relevance of the positive reactions (1+ through 3+) was determined and categorized as certain, probable, possible or not relevant. Contact allergy was defined as clinically relevant according to the following criteria: (i) certain exposure to the sensitizer and (ii) the patients dermatitis can be explained by the exposure (8, 11, 14, 15).

A standardized history (including sex, age, occupation, exposures) together with the primary site of dermatitis were carefully noted. At the same time the patients were interviewed about their history of adverse reactions to fragrances or cosmetic products.

Each patient was assigned to one of four categories according to their history of fragrance intolerance. The first category was 'Certain'; the patient had reacted with an itching dermatitis to at least one fine perfume or aftershave and had reacted to other scented products. The second category is 'Probable'; the patient had reacted to one or more scented products (e.g. deodorant) but a specific perfume had not been identified as the cause of a clinical reaction. The third category was 'Questionable'; the patient had reacted to various cosmetics with or without fragrances. Materials other than fragrance constituents could have been the cause of a reaction in this category of patients. And the last category is 'None'; the patient had never reacted to a scented material.

Results

Frequencies of sensitization

A total of 320 patients was patch tested with a mean age of 39 years (range: 2–85 years). There were 231 women tested (72.2%) and 89 men (27.8%). Most of these patients had eczema of the face or hands (Table 3). We found a total of 76 positive reactions in 33 patients (19 women, 14 men), which means that 10.3% of all patients tested (women 8.2%, 19 out of 231; men 15.7%, 14 out of 89) had one or more positive reactions to fragrance ingredients. Of the 76 positive reactions, 51 (67.1%) were found in women and 25 (32.9%) in men. Most positive reactions were 1+ (61; 80.3%). Of these 1+ reactions 38 were found in the group of women (62.3%) and 23 in the group of men (37.7%). There were 14 (18.4%) ++ reactions of which 12 were found in the group of women (85.7%) and 2 in the group of men (14.3%). And there was only 1 +++ reaction (1.3%; with a woman).

The results of patch testing to the individual fragrances are listed in Table 1. Most positive reactions were seen to hydroxyisohexyl 3-cyclohexene carboxaldehyde with 3.1%, *Evernia furfuracea* and cinnamyl alcohol (2.5%), hydroxycitronellal (2.2%), *Evernia prunastri* (1.9%), cinnamal (1.6%), eugenol and isoeugenol (1.3%). We did not find any positive reactions to amyl cinnamal, anisyl alcohol, benzyl benzoate, benzyl cinnamate, and d-limonene. The total number of irritant reactions was 30 (21 in women, 70%; and 9 in men, 30%). These irritant reactions were found in 16 (5%) patients (12 women, 5.2% of the women; 4 men, 4.5% of the men). Most irritant reactions were observed to *Evernia furfuracea* with a frequency of 1.3% (4 out of 320 patients), and farnesol with a frequency of 0.9% (3 out of 320). There were 12 doubtful reactions at D3. At D7 after start of the test, only one of these reactions was

Table 2. List of primary localization of eczema and frequency of sensitization

Localization	Number of patients	Frequency (n = 320)	% Positive reactions EU-list (n = 33)
Face	79	24.7%	15.6
Hands	78	24.3%	25.0
Periorbital	52	16.3%	6.3
Neck	25	7.7%	9.4
Trunk	21	6.7%	6.3
Generalized	16	5.0%	12.5
Arms	14	4.3%	9.4
Armpits	11	3.3%	9.4
Scalp	11	3.3%	0
Feet	7	2.3%	0
Legs	6	2.0%	6.3

Number of patients tested (n); Primary localization of eczema of patients with a positive reaction to one or more fragrances of the EU-list (% Positive reactions EU-list).

positive (hydroxycitronellal), while the rest was negative.

The primary site of the eczema of the patients in this study was in most cases the face, hands, or periorbital, respectively, 24.7%, 24.3%, and 16.3% (Table 2). The highest percentage of positive patch test reactions was found among patients with a primary location of the eczema of the hands (25.0%), followed by eczema of the face (15.6%).

Discrepancies between FM I, FM II and the 26 fragrance compounds

The FM I was patch tested in 295 patients (Table 3). We found a frequency of positive reactions to the FM I of 5.8% (17 out of 295 patients). A total of 11 patients (3.7%) showed one or more positive reactions to the EU-list and also to the FM I. Twenty patients (6.8%) did react to one or more ingredients of the EU-list but did not show a positive reaction to the FM I, and six patients (2.0%) did have a positive reaction to the FM I but not to a ingredient of the EU-list.

In 227 patients the FM II was patch tested (Table 3). We found a frequency of sensitization to the FM II of 9.3% (21 out of 227 patients). A total of 14 patients (6.2%) had positive reactions to one or more ingredients of the EU-list as well as to the FM II. Twelve patients (5.3%) appeared to have at least one positive reaction to the EU-list but no positive reaction to the FM II, and seven patients (3.1%) did have a positive reaction to the FM II but not to one of the ingredients of the EU-list.

When the FM I as well as the FM II were patch tested (Table 2) it appeared that 17 patients (7.5%) had one or more positive reactions to the ingredients of the EU-list and also to the FM I and/or the FM II. A total of 9 (4.0%) patients showed a positive reaction to the EU-list but not to the FM I and/or

Table 3. Reactions to fragrances of the EU-list and Treemoss in relation to reactions to FM I and FM II

		FM I		FM II		FM I and/or FM II	
		Positive	Negative	Positive	Negative	Positive	Negative
Total number, <i>n</i>		295		227		228	
EU-list	Positive	11	20	14	12	17	9
	Negative	6	258	7	194	12	190
Total number, <i>n</i>		295		227			
<i>Evernia furfuracea</i>	Positive	5	2	3	3		
	Negative	12	276	18	203		

Fragrance mix I (FM I); Fragrance mix II (FM II); Both FM I and II are patch tested (FM I and/or FM II); Total number of patients tested (*n*), Number of patients with positive patch test reactions (Positive); number of patients with no positive patch test reactions (Negative).

FM II, and 12 patients (5.3%) did have a positive reaction to the FM I and/or FM II but not to an ingredient of the EU-list.

Table 3 also shows the percentages of positive and negative reactions to *Evernia furfuracea* as a single ingredient compared to the reactions to the FM I and FM II. A total of five patients (1.7%) had a positive patch test reaction to *Evernia furfuracea* as well as to FM I, and three patients (1.3%) to *Evernia furfuracea* and FM II. A total of two patients (0.7%) showed a positive reaction to *Evernia furfuracea* but not to the FM I and three patients (1.3%) had a positive reaction to *Evernia furfuracea* but not to FM II.

Clinical relevance

In 20 out of 33 (60.6%) patients with one or more positive patch test reactions a certain clinical relevance of the positive reactions was established, 12.1% (4 out of 33) of the reactions was judged as probably clinically relevant, 21.2% (7 out of 33) possibly and in only two patients (6.1%) the positive reactions were unlikely or not clinically relevant.

History of adverse reactions

A total of 247 patients were interviewed about their history of adverse reactions to fragrances or cosmetic products. The outcome of this interview is shown in Table 4. Most patients (57.1%) could not recall an adverse reaction to fragrances or cosmetic products, 19.0% of the patients did have a certain history of adverse reactions. Of these patients with a certain adverse reaction to fragrances in their history 46.4% showed also a positive patch test reaction. Nine (32.1%) patients showed a positive patch test reaction but never had reported an adverse reaction to fragrances or cosmetic products.

Discussion

The aims of this study were to describe the frequency of contact allergy to the fragrances of the

Table 4. History of adverse reactions to fragrances or cosmetic products combined with results of patch testing 26 fragrances

	Patient history, % (<i>n</i>)	Positive patch test reaction to fragrances, % (<i>n</i>)	% of positive reaction in relation to their history
Total number, <i>n</i>	247	28	28
Certain	19.0 (47)	46.6 (13)	27.7
Probable	13.0 (32)	3.6 (1)	3.1
Questionable	10.9 (27)	17.9 (5)	18.5
None	57.1 (141)	32.1 (9)	6.4

Number of patients (*n*), Number of patients tested (Total number, *n*).

EU-list, to evaluate the clinical relevance of the positive patch test reactions and to investigate if testing with the EU-list has an additional benefit in the diagnostic patch test procedure. The major outcomes of this study are that we found a high frequency of contact allergy to fragrances of the EU-list of 10.3%, with most positive reactions to hydroxyisohexyl 3-cyclohexene carboxaldehyde, cinnamyl alcohol and surprisingly *Evernia furfuracea*. The clinical relevance of these positive reactions was 61%. If only FM I and FM II were patch tested, 4% of all patients tested with a contact allergy to fragrances would be missed.

Previous studies on patch testing with FM I and FM II as a screening tool for contact allergy to fragrances have reported a frequency of 6.5% of the patients reacted to FM I and 2.9–4.6% of the patients reacted to FM II (8, 11, 16, 17). We found a frequency of sensitization to the list of 26 fragrances of 10.3%. Interestingly, we found a difference in frequency of sensitization between men and women (15.7% versus 8.2%), while in the literature it has been described that in eczema patients, the male:female ratio of FM I allergy is usually 1:2 (18, 19). A more equal distribution between males and females is seen in the general population, especially in the younger age groups (20).

We showed most positive patch test reactions to hydroxyisohexyl 3-cyclohexene carboxaldehyde

with a frequency of 3.1%. Hydroxyisohexyl 3-cyclohexene carboxaldehyde is not part of the FM I. Several recent studies have reported that hydroxyisohexyl 3-cyclohexene carboxaldehyde is one of the most frequent sensitizers in the past years, giving positive reactions in 1–2.9% of patch tested patients (3, 10, 11, 21–23). Results on patch testing the 26 fragrances of the EU-list have also been published by Schnuch et al. in 2007 (10). They showed a frequency of sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde of 2.3%. In our study we found an even higher percentage of 3.1% positive patch test reactions to hydroxyisohexyl 3-cyclohexene carboxaldehyde. Striking is the high percentage (2.5%) of patients with positive patch test reactions to *Evernia furfuracea* in our study. Schnuch and co-workers were the first who tested *Evernia furfuracea* in a larger unselected population (10). They found a similar percentage of 2.4%. In their study it was even the most frequent allergen followed by hydroxyisohexyl 3-cyclohexene carboxaldehyde, although they used unselected patients. These comparable results seem to show that the high percentage of positive reactions to *Evernia furfuracea* we found may not be due to the fact that a different vehicle was used. *Evernia furfuracea* is not part of FM I or FM II and is therefore not used as a screening agent for contact allergy to fragrances. Our study showed that 2 out of 295 (0.7%) tested had a positive reaction to *Evernia furfuracea* but were missed by testing only with the FM I and 3 out of 227 (1.3%) of the patients who were positive to *Evernia furfuracea* were missed by testing only FM II. Perhaps *Evernia furfuracea* is used in a lot of perfumed products and therefore the high frequency of contact allergy to *Evernia furfuracea* can be explained. Cinnamyl alcohol seems to be converted in the skin to the chemically related cinnamal. Cinnamal is known as a strong allergen and has been one of the highest ranking fragrance allergen for many years, but recently there is a striking reduction in the frequency of sensitivity to cinnamal (with 18% yearly) and also cinnamyl alcohol. They are nowadays considered as uncommon allergens (18, 24, 25). However, our study shows that sensitization to cinnamal as well as cinnamyl alcohol is still common in our eczema patients with frequencies of 1.6% versus 2.5%. Previous studies reported for isoeugenol a sensitization frequency of 1.7% and 1.1%, which is comparable to the 1.3% in our study (10, 26). Eugenol was classified as a less important allergen, although frequently used, by a recent study of Schnuch et al. (10). They found a sensitization frequency of only 0.4% while our study showed that eugenol was one of the common allergens with a frequency of 1.3%. This difference in

positive reactions may be explained by the higher concentration of 2% used by us.

Interestingly, the single ingredients of FM I and II and *Evernia furfuracea* are the highest ranking allergens of the total of 26 fragrance ingredients tested except for citronellol and amyl cinnamal. Citronellol is part of FM II and previous studies showed frequencies of sensitivity of 0.2–0.5% (10, 11, 22). In this study we found a comparable frequency of 0.3%. We found no positive patch test reactions to amyl cinnamal which is part of FM I. A previous study of Schnuch et al. showed also a frequency of positive patch test reactions of only 0.1%, which suggests that amyl cinnamal is not a frequent sensitizer these days (10). Also the other fragrance ingredients to which we found no positive patch test reactions (anisyl alcohol, benzyl benzoate, benzyl cinnamate, and d-limonene) can be regarded as uncommon allergens. D-limonene and linalool were used unoxidized. Different studies have now proved that both d-limonene and linalool as pure compounds seldom cause positive patch test reactions. However, their oxidation products have been shown to cause contact allergy (27–35). There may have been a certain degree of oxidation during the storage of our patch test preparations.

In this study we found that if the FM I is tested alone, 20 patients with a contact allergy to one or more fragrance ingredients will be missed. If the FM II is tested, 14 patients will be missed. If FM I and II are tested, nine patients with a contact allergy fragrances will still be missed.

We showed that FM I and II, when tested together, are important as a screening test for contact allergy to fragrances. In this study we found that in 60.6% of the patients with positive patch test reactions the clinical relevance was judged as certain. As far as we know, this is the first study where clinical relevance of positive patch test reactions was evaluated in this way. It is assumed that the percentage of clinically relevant reactions in patients suspected of a contact allergy for fragrances lies between the 50% and 65% (1, 2). Still 21.2 % of the sensitized patients had positive patch test reactions that were possibly clinically relevant and 6.1% of the patients had no clinically relevant contact sensitization. Although there are a lot of studies that report the frequency of positive patch test reactions to fragrances, the assessments of the relevance of these reactions were not always clear, or different methods were used (1, 6, 11, 36, 37).

Of all patients questioned about their history of adverse reactions to fragrances or other cosmetic products, most people (57.1%) were unaware of any adverse reaction. However 19% of the patients interviewed did have a certain adverse reaction in their history. De Groot et al. (1) found that 12% of the

general population reported an adverse reaction to cosmetics or toiletries in the past 5 years. Of these 12%, another 35% of these patients (4.3% of the total population) attributed this adverse reaction to products used for their odour, such as deodorants, aftershaves, and perfumes. Of our patients with a history of adverse reactions 27.7% also had one or more positive patch test reactions and were recognized as sensitized to fragrances. This means that the rest of this group (72.3%) may have had an adverse reaction to other ingredients of scented products like preservatives.

In conclusion, we found a high frequency of contact allergy to fragrances by using all the 26 fragrance allergens labelled on products in the EU. The most important sensitizers are ingredients of FM I, FM II and also the single ingredient *Evernia furfuracea*. Compared to the complete EU-list screening for patients with a contact allergy for fragrances with the FM I and FM II some patients will be missed. Therefore, it seems necessary to include *Evernia furfuracea* in one of these fragrance mixes. Testing with *Evernia furfuracea* in to FM I and II identifies fragrance allergy in an additional 4% of the population that has been tested. Interesting is the difference we found between the clinical relevance of positive reactions and the patients' history of adverse reactions to fragrances: the patients' histories indicated fewer adverse reactions to fragrances than the number of reactions with clinical relevance according to the doctor's assessment.

If a patient has a positive patch test to one of the fragrance mixes, it is unknown which single ingredient caused this positive reaction. Therefore, it is helpful to test with a list of single ingredients like the EU-list. Our study confirmed the findings of Schnuch et al. (10) who showed very low frequencies of sensitization to some fragrance compounds which indicates that these compounds may not be common allergens. These findings suggest that in the future the EU-list may need revision. However, only two studies have been published thus far on patch testing the 26 single ingredients of the complete EU-list. It is highly recommended that more studies in different European populations should be performed, as there might be differences in contact allergy to fragrances in different countries.

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